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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/761,370	01/22/2004	David Wallach	WALLACH=27A	3756

1444 7590 02/10/2006

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EXAMINER
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RIGGINS, PATRICK S

ART UNIT	PAPER NUMBER
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1633

DATE MAILED: 02/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/761,370

Applicant(s)

WALLACH ET AL.

Examiner

Patrick S. Riggins

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 03 January 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1 and 5 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1 and 5 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 22 January 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☒ Certified copies of the priority documents have been received in Application No. 09/646,403.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 1/22/04.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: Notice to Comply.

## **DETAILED ACTION**

### ***Election/Restrictions***

1. Applicant's election without traverse of Group I, claims 1 and 5, in the reply filed on 1/3/06 is acknowledged.
2. In the Response to Election/Restriction filed 1/3/06, Applicant canceled all claims drawn to the other groups. Thus, claims 2-4 and 6-16 were canceled. Presently claims 1 and 5 are pending and under examination.

### ***Priority***

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09646,403, filed on 2/21/01.

### ***Specification***

4. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
5. The disclosure is objected to because of the following informalities: Several of the Brief Descriptions of the Drawings do not properly refer to each panel of the figure. Specifically, the Brief Description of Figure 4 should refer to --Figures 4A-4C--, Figure 5 should refer to --Figure 5A-5B--, Figure 6 should refer to --Figure 6A-6B--, and Figure 9 should refer to --Figure 9A-9B--. Figure 3 contains sequences. As such either Figure 3 should be amended to identify SEQ ID

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NOs or the Brief Description of Figure 3 should be amended to refer to the appropriate SEQ ID NOs.

Appropriate correction is required.

6. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Figure 3 contains sequences that were not included in the Sequence listing. Additionally, paragraph 0171 comprises a sequence that must be included in the Sequence listing, with appropriate amendment of the specification to refer to the appropriate SEQ ID NO. Further throughout the Examples, reference to sequences of the invention, refer only to the Figure in which the sequences appear. To fully comply with the Sequence requirement, these references to sequences should also include reference to the appropriate SEQ ID NO. A specific example of this is in paragraphs 0217 and 0218, sequences are referred to only in reference to being shown in Figure 1 or Figure 2. This must also include a reference to the appropriate sequence in the sequence listing.

Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Applicant is requested to return a copy of the attached Notice to Comply with the reply.

***Claim Rejections - 35 USC § 112***

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claim 1 and 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. The claim recites that “whose protein sequence is that of SEQ ID NO: 4”. This is vague and indefinite because the recitation of SEQ ID NO: 4 appears to be for the full length sequence, but by reciting “that” this opens up the possibility for unsupported fragments of the sequence. Thus the skilled artisan could not ascertain the metes and bounds of this limitation in the claim. It would be remedial to delete “that of”.

10. Claim 1 is further drawn to an antibody against RAP-2 “or a derivative thereof”. This is vague and indefinite because there is no clear definition as to what is intended by an antibody derivative. It is possible that this term could be construed to encompass any protein with a capability of binding. His clearly is not any appropriate form of antibody and was clearly not contemplated in the specification. With this usage of the vague and indefinite term “derivative” of an antibody, the skilled artisan would be unable to ascertain the metes and bounds of this limitation in the claim.

11. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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12. Claims 5 include the limitation that the antibodies could be used in a formulation for extracellular application. As RAP-2 is an intracellular protein, it is wholly unclear how one would practice this method in the context of a formulation for external application. Indeed in paragraph 0159, the specification indicates that “the RAP-2 protein is entirely intracellular (as suspected)”. Additionally, Li (Proc Natl Acad Sci USA 96: 1042-1047 (1999), of record), a study by the applicants where RAP-2 is referred to as FIP-3, FIP-3 is clearly shown to be intracellular (see Figure 2, and the paragraph bridging columns 1 and 2 of page 1044). From this, the skilled artisan would be unable to ascertain the metes and bounds of this limitation in the claim.

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

15. Claim 1 recites the antibody is specific for RAP-2 protein, whose sequence is “that” of SEQ ID NO: 4. This claim language encompasses “isoforms, analogs, fragments or derivatives” of RAP-2 (see paragraph 0025 lines 2 and 3).

16. The claim embraces a genus of RAP-2 proteins that are not recited in any specific structure, which is crucial for the making of an antibody specific to RAP-2 protein. The as-filed

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specification only provides sufficient written description of the amino acid sequence set forth in SEQ ID NO: 4. However, the claim is broadly drawn to RAP-2 protein species such as isoforms, analogs fragments, or derivatives, as described above in paragraph 15, essentially fragments of RAP-2, which have yet to be identified or discovered.

17. In view of the reasons set forth in the preceding paragraphs, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is part of the invention and reference to potential methods and/or assays and/or any other unspecified structure containing unspecified compounds and/or packaging agents that are only described by functional language, wherein the detailed and common structure of the genera of the claimed compounds was not described; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structure(s) of component(s) that are linked structurally in order to exhibit the disclosed biological functions as contemplated by the as-filed specification.

18. Claiming unspecified molecular structures of material(s) as fragments of RAP-2 protein-specific antibodies, which must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would

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recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). Therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification.

19. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the antibodies against unspecified fragments of SEQ ID NO: 4 as presently claimed. Deletion of the phrase “that of” would be remedial to obviate the present rejection.

20. Claim 5 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

21. The claim is drawn to a method for modulating RIP-mediated effects on cells by treating with a composition comprising an antibody against RAP-2. The composition can be applied either to the extracellular surface to contact extracellularly exposed RAP-2 or applied internally to the cell in a composition suitable for intracellular application. In order to practice this method of the invention, the skilled artisan would be required to undertake an undue level of experimentation.

22. A number of factors have been considered in making this assertion that undue experimentation is required to practice this invention as delineated by *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in



the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

23. Initially it is noted that the claim encompasses a method using a composition suitable for extracellular application. As established above in paragraph 9, RAP-2 is expressed intracellularly and thus could not be contacted on the extracellular surface of the cell. Therefore this embodiment of the claim would seem to be non-functional. As such, a nearly unimaginable level of experimentation would be required of the skilled artisan to practice this embodiment of the claimed invention.

24. Considering the intracellular embodiments, the claim is drawn to modulation of RIP activity by application of an antibody intracellularly. In order to do so, one would be required to determine a delivery method, the levels of antibody necessary to see the desired effect, and a suitable assay in order to determine if the antibody composition applied intracellularly was indeed affecting RIP activity. Therefore the questions at hand are as follows: would an antibody, which is normally expressed in the extracellular milieu, have sufficient stability if intracellularly expressed to perform the desired function? Is there sufficient evidence to ensure that if a functional antibody against RAP-2 were delivered intracellularly that effects on RIP activity would be observed? The specification is generally silent about these issues, as the predominant assays contemplated using antibodies were *in vitro* in nature, i.e. for use in the purification or RAP-2, for staining of tissues sections, or for Western blotting or ELISA (see for example, paragraph 0192). Though not presently within the scope of the instant claim, it is noted that it is unclear how the antibodies of the invention would be used in diagnostic screens (e.g. in

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paragraph 0031), as disorders associated with aberrant RAP-2 expression have not been disclosed.

25. Regarding intracellular use of an antibody, the specification is largely silent regarding issues that may be present in regard to stability or functionality of intracellularly expressed antibodies. The prior art however clearly establishes that the use of antibodies intracellularly is fraught with many potential problems.

In principle, intrabodies can be directed to all intracellular compartments by encoding the corresponding signal sequence attached to the antibody fragment. Among these different intracellular locations, expression in the cytoplasm is the most difficult task, because of its reducing environment. This reducing potential prevents the formation of disulfide bonds, including the conserved intradomain disulfides in antibody domains. Indeed, it was found that scFv fragments expressed cytoplasmically in COS cells do not form disulfide bonds. The intradomain disulfide contributes about 4-5 kcal/mol to the stability of antibody domains. Therefore, antibody fragments expressed in a reducing environment are strongly destabilized, compared with the same molecules containing disulfides, and a smaller fraction of these fragments is likely to fold to the correct native structure. This fact is believed to be responsible for the frequently observed reduced antibody fragments, as well as for their high tendency to form aggregates [references omitted throughout].

J Biol Chem 275: 2795-2803 (2000), newly cited,  
page 2795, column 2, second full paragraph

Thus the prior art clearly establishes that it is highly unpredictable if any given antibody or antibody fragment will be functional in the intracellular milieu.

26. We next question what the likelihood is that a functional intracellular antibody against RAP-2 would necessarily affect RIP activity. The specification clearly established that RAP-2 can interact with RIP (see Examples 1-3). The specification further establishes that RAP-2 does not interact with TRADD, MORT, p55-TNF receptor, p75-TNF receptor, MACH, lamin, or cyclin D (see paragraph 0231). From this applicants conclude "RAP-2 protein possible interacts with RIP in a very specific manner and as such it represents a specific modulator/mediator of RIP" (paragraph 0232).

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27. Despite this proclamation, further passages in the specification and information gleaned from the art calls in to question how specific the action of RAP-2 is for RIP. In this regard, in paragraph 0230, the specification states in regard to a RAP-2 RIP interaction: “ However, formation of such a complex did not result in RIP enzymatic activity: to the extent we could judge by an *in vitro* immunocomplex kinase assay, over-expressed RIP did not phosphorylate RAP-2”. Also, the specification shows that RAP-2 has other affects in a cell aside from direct effects on RIP, such as the interaction with NIK, the IKK complex, TIP60, and seemingly direct effects on both NF- $\kappa$ B and c-Jun-dependent transcription (see Examples 4-7).

28. Further in this regard, shortly after applicants’ cloning of RAP-2 a group cloned the mouse homolog to RAP-2 (Cell 93: 1231-1240 (1998), of record, hereinafter Yamaoka) called NEMO and another group independently cloned RAP-2 from human cells (Nature 395: 297-300 (1998), of record, hereinafter Rothwarf) and called it IKK $\gamma$ . Yamaoka and Rothwarf identified NEMO and IKK $\gamma$ , respectively as a component of the I $\kappa$ B kinase complex. From this it would seem much more likely that antibodies directed against RAP-2 would have effects on IKK activities, not specifically on RIP activities. Indeed the specification seems suggest that RAP-2 functions go beyond affecting RIP activity. “Remarkably, the fact that RAP-2 is able to exert is effects as far down the signal transduction pathway as RelA, implies that part of this protein action could be common to various, and otherwise divergent signaling pathways” ( bottom of the first page containing paragraph 0234).

29. It is also notable that the nature of RAP-2 function does not appear to have been fully ascertained at the time of the invention and as such the skilled artisan would be forced to determine what effects on RIP would be expected in the practice of the invention. In paragraph

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234, RAP- is suggested to downregulate NF- $\kappa$ B activation induced by RIP or NIK. In paragraph 0235, it is established that RAP-2 at low levels can have a stimulatory effect on TRAF-2-mediated NF- $\kappa$ B activation. With these seemingly conflicting results it is unclear how the skilled artisan would be convinced that antibodies against RAP-2 would necessarily influence RIP activity without further experimentation to ensure that RAP-2 modulation would indeed result in effects on RIP activity.

30. Additionally in this regard, even if one were to grant that anti-RAP-2 antibodies would modulate RIP activity, a point not conceded, there is no real description in the specification as to the assays one would perform in order to measure RIP activity. There is no basis describing how anti-RAP-2 antibodies would lead to changes in RIP activity, as described above. But with the wide array of possible effects of RIP (see paragraph 0025) how would the skilled artisan know what portion of RIP activity to observe to determine whether any RIP modulation had occurred? In order to determine these details would indeed be an additional level of experimentation that would be required of the skilled artisan, thus further establishing the overall undue level of experimentation that would be required to practice the invention.

31. When determining if an enablement rejection is proper, one first looks to the specification to determine if there is sufficient disclosure to permit one of skill in the art to practice the invention. In the instant case, the specification is silent regarding identification of antibodies that would be functional in an intracellular environment. Further, the specification has not convincingly established a conceptual framework that would allow one to treat with antibodies against RAP-2 and confidently expect to see effects on RIP activities. One then looks to the art to determine if the knowledge existed at the time of the invention which would address any

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information that was absent from the specification. In the instant case, the prior art is silent on RAP-2 effects on RIP, as RAP-2 is a novel protein in the art. Subsequent studies, i.e. Yamaoka and Rothwarf cast serious doubt on the idea that RAP-2 is a direct mediator of RIP functions.

32. Finally one considers what level of experimentation would be required in order for the skilled artisan to practice the invention. In the instant case, the skilled artisan would need to perform experimentation to overcome several likely obstacles. First undue levels of trial and error type experimentation would be required to identify antibodies against RAP-2 or fragments thereof that would function in the intracellular milieu. Identification of such antibodies is by no means guaranteed. Secondly, the skilled artisan would be required to perform undue levels of experimentation in order be certain that intracellularly delivered RAP-2 antibodies would necessarily lead to effects on RIP activity and to further perform undue levels of experimentation to determine the nature of RIP activity that was to be monitored for the assay as claimed. Thus, the specification does not enable the skilled artisan to practice the method of claim 5 in the absence of undue levels of experimentation.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patrick S. Riggins whose telephone number is (571) 272-6102. The examiner can normally be reached on M-F 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patrick Riggins, Ph.D.  
Examiner  
Art Unit 1633

  
**DAVE TRONG NGUYEN**  
**SUPERVISORY PATENT EXAMINER**

<b>Notice to Comply</b>	Application No.	Applicant(s)	
	10/761,370	WALLACH ET AL.	
	Examiner	Art Unit	
	Patrick S. Riggins	1633	

**NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES**

Applicant must file the items indicated below within the time period set in the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other: Not all sequences disclosed in the specification appear in the sequence listing.

**Applicant Must Provide:**

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", **as well as an amendment specifically directing its entry into the application.**
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (571) 272-2510

For CRF Submission Help, call (571) 272-2501/2583.

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